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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,274	10/09/2007	**Rehab Al-Jamal**	MUR-06-1101	9435

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
01/28/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/576,274	AL-JAMAL ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,15,16 and 19-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 15-16 and 19-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/28/2009 has been entered.

2. Claims 1, 4, 15-16 and 19-30 are pending and under examination in the instant application.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 4, 15-16 and 19-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Actions mailed 12/03/2008 and 07/28/2009.

Applicant is in possession of a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a.

Applicant is not in possession of the methods recited in claims 1, 4, 15-16 and 19-30.

Applicant's arguments, filed 12/28/2009, have been fully considered, but have not been found convincing.

Applicant asserts that the present application provides an adequate written description of the recited compounds as it provides a precise definition and description of the compounds of claims as if provides a precise definition and description of the compounds of the claims. This definition and description provides relevant, identifying characteristics of the compounds in the form of functional characteristics coupled with the disclosure of a correlation between function and structure. Applicant submits that the functional characteristics of the compound is the modulation of the function of beta 1 integrin by the compound resulting in at least one of (i) an

inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (ii) an increase in the anabolism of the extracellular matrix. The present application provides a screening method to identify compounds which possess these functional characteristics. Applicant asserts that there is a correlation between function and structure. In particular, the application discloses a relationship between the desired functional characteristics and a structure which binds to the beta 1 integrin molecule in the region of amino acid residues 82-87 comprising residues TAEKLIK (SEQ ID NO:1) of the sequence of the mature beta 1 integrin molecule. Applicant further asserts that the issue of "no described or art-recognized correlation or relationship between the structure of recited compounds and their beta 1 integrin modulation function is error as there is a relationship between the structure of the recited compounds and their beta 1 integrin modulation function—the relationship being that the compound must bind the region of amino acid residues 82-87 of the sequence of the mature beta 1integrin molecule comprising residues TAEKLK in order to have the desired beta 1 integrin modulation function. Applicant points to the specification on page 11, line 26 to page 12, line 3 which discloses that each domain of beta 1 integrin appears to possess a different function. Hence, binding to different domains may entail different downstream intracellular signaling resulting in different functional outcomes. Applicants submit that the present application identifies the specific domain to which the compound for use in the present invention must bind, and thus describes a relationship between the structure of the recited compounds and their beta 1 integrin modulation function. Applicant concluded that one of ordinary skilled in the art could therefore instantly envisage, based on the present disclosure, a genus of compounds each of which bind the identified region of beta 1 integrin and retain the essential functional features. Applicant submits that the specification provides a precise definition of the recited compound, that the definition provided functional characteristics coupled with the disclosure of a correlation between function and structure, and that this is sufficient to show the Applicants were in possession of the recited genus of compounds identified in the claims. Applicant concluded that the specification provides an adequate written description and that the recited compounds are described in the specification in such a way as to reasonably convey to one of ordinary skill in the art that they, at the time the application was filed, had possession of the subject matter of the claims. Moreover, Applicant submits that the definition of the recited compounds differs from the definition of the compounds in the case of Univ. of Rochester V. G.D. Serale & Co. in that the recited compounds are defined as binding to a specific site and this binding correlates to the desired functional activity of the compounds. In contrast, the definition provided in the case of Univ. of Rochester V. G.D. Serale & Co. appears to have been solely in terms of functional activity.

Besides the monoclonal antibody produced by the commercial clone JB1a, the specification does not describe an actual reduction to practice of a compound that modulate beta 1 integrin through its binding to TAEKLK. The specification also does not describe the complete structure of a compound that functional modulation of beta 1 integrin that results in at least one of (i)-(iii). Further, the specification does not describe the partial structures or physical properties, or chemical properties of a compound that functional modulation of beta 1 integrin. While the specification describes the amino acid sequence of the beta 1 integrin molecule in a region of amino acid residues 82-87 comprising residues TAEKLK, the specification does not describe any correlation between the sequences and the structure of any compounds that would functional

modulation of beta 1 integrin which would result in at least one of (i)-(iii) claimed in claim 1. The specification describes a method of screening compounds for functional modulation of beta integrin which would result in at least one of (i)-(iii) in claim 1, however there is no information regarding what structural features would likely be associated with such functional modulation. Accordingly, the specification does not disclose a correlation between functional modulation and the structure of a putative compound. Thus, the specification fails to satisfy the written description requirement of 35 U.S.C 112, first paragraph, with respect to written description. Like the compounds of Rochester (issued U.S. Patent No. 6,048,850), which is directed to a method of selectively inhibiting the COX-2 form of the enzyme by administering a non-steroidal compound that selectively inhibits activity of the COX-2 gene product, the instant compounds in the claimed methods binds to the beta 1 integrin molecule in a region of amino acid residues 82-87 comprising residues TAEKLK and functional modulation of beta 1 integrin results in at least one of (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix. Defining written description in the context of biotechnology and pharmaceuticals, *Regents of University of California v. Eli Lilly & Co.,* 119 F.3d 1559 (Fed. Cir. 1997) held that a description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." In *University of Rochester v. G.D. Searle & Co.,* the court concluded that, as a matter of law, the patent at issue clearly and convincingly proved its own invalidity where the required compound was not disclosed and where there was no pre-existing awareness in the art of a compound exhibiting the claimed activity. *University of Rochester v. G.D. Searle & Co.,* Case No. 03-1304 (Fed. Cir., Feb. 13, 2004).

6. Claims 1, 4, 15-16 and 19-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting tissue repair in lung emphysema comprising administering the monoclonal antibody produced by commercial clone JB1a or antibodies that binds TAEJKJ of SEQ ID NO:1, does not reasonably provide enablement for methods claimed in claims 1, 4, 15-16 and 19-30. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reason set forth in the previous Office Actions mailed 12/03/08 07/28/2009.

Further, the burden of enabling the prophylactic treatment (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those mammals susceptible to such diseases and the difficulty of proof that the administration of the drug was the agent that acted to prevent the condition. Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to tissue injury within the scope of the presently claimed invention. Nor is sufficient guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed compounds including anti-β1 antibody in preventing tissue injury state.

Applicant's arguments, filed 12/28/2009, have been fully considered, but have not been found convincing.

Applicant submits that the present specification describes structural and functional characteristics of the compounds of the claims. The structural features are the sequence of the beta 1 integrin molecule to which the recited compounds bind. The functional characteristics are the ability to modulate beta 1 integrin activity and produce at least one of (i) an inhibition of the apoptotic pathway, (ii) an alteration in the metalloproteinase balance or (iii) an increase in the anabolism of the extracellular matrix. Applicant submits that one of ordinary skill in the art would have no difficulty in obtaining compounds which bind to the identified region of the beta 1 integrin molecule and modulate its function as described. Such compounds, for example, may include other antibodies in addition to the JB1a antibody. As indicated in the description of the present application at page 31, lines 16-21, antibodies for use in compositions and methods of the claims can be readily prepared without undue experimentation. This is routine, where the epitope is known (as it is here), and such antibodies can be easily prepared by one of ordinary skill in the art according to standard techniques and procedures for immunizing animals, such as mice, with protein epitopes and the selection of hybridomas that produce immunogen specific monoclonal antibodies. The applicant further submits that the recited compounds are not restricted to antibodies, but may also include, for example, synthetic peptides. Applicant concluded that one of ordinary skill in the art would automatically know how to make such a peptide which binds the identified region of the beta 1 integrin molecule without undue experimentation using well known techniques. A person of ordinary skill in the art could then, without undue experimentation, use the screening methods disclosed in the application to select from the antibodies/peptides which bind the identified region of beta 1 integrin and those which have the desired modulatory effect on the function f beta 1 integrin. The Applicants therefore submit that the present application teaches one of ordinary skill in the art how to make and use the recited compounds without undue experimentation. Stated differently, the applicants submit the full scope of the claims is enabled.

However, besides the anti-TAEKLK antibodies, the specification fails to enable the method by using compounds that binds to TAEKLK of beta 1, wherein the compounds yet to be identified. The specification further fails to provide guidance on compounds that inhibit the apoptotic pathway, alter (increase or decrease) in the level of metalloproteinase balance or increase in anabolism of the extracellular matrix. Again, while "compounds" that inhibit the apoptotic pathway, alter (increase or decrease) in the level of metalloproteinase balance or increase in the anabolism of the extracellular matrix may have a notion of "inhibiting" the function of the claimed beta 1 integrin; there is insufficient biochemical or structural information to enable the skilled artisan to make and use the "compounds", as broadly claimed. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

While the specification on page 31, lines 16-22 discloses preparation of antibody is a standardized technique, however, it is unpredictable whether the resultant antibodies that bind to ^{82}TAEKLK^{87} epitope of the β1 integrin molecule would be allosteric modulation of beta1 integrin. For example, Al-Jamal and Harrison teach three antibodies that bind to epitope 82-87 of β1 integrin that has function blocking effects, but only JB1a has the allosteric modulation properties (see table 1). Al-Jamal and Harrison teach that JB1a antibody clone could recognize a conformational dependent epitope and its functional effect is a partial allosteric inhibitor (see page 85, 2nd col., 4th ¶). Al-Jamal and Harrison teach that although the epitope of the JB1a maps to the hybrid region, there is a possibility that it may recognize another sequence in the A domain almost sandwiched between the MIDAS and the ADMIDAS. Whether the real epitope could be discontinuous and/or combinational, remains unclear (see page 89, 2nd col., 4th ¶). With respect to synthetic peptides, neither Applicant nor the prior art has identify any synthetic peptides that would function like clone JB1a, i.e., allosteric modulation of β1 integrin. No synthetic peptides have been shown to bind conformational epitope or the hybrid region of β1 integrin. Therefore, one skilled in the art at the time of the invention would not be able to predict which compounds such as antibodies or synthetic peptides will result in functional modulation of beta 1 integrin. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. While experimental testing techniques using cell surface receptor binding compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

Applicant submits that the specification on page 11, line 17 to page 12, line 13 explains that integrins have several functions. The Applicants submit the same compound may serve to inhibit one function of beta 1 integrin and to stimulate another function. This is supported by the declaration under 37 CFR 1.132 by Dr. Rehab Al-Jamal, one of the inventors of the claimed subject matter. This declaration includes experimental data (Appendix B) supporting the role of the anti-beta1 antibody, JB1a, as both an agonist and an antagonist which is demonstrated by its effect on downstream signaling with and without injury and its conformation effect from the FRET. As noted on page 12, lines 8 to 13 of the present specification, the use of the functional modification terminology serves best to take this dual function as an agonist and an antagonist of beta 1 integrin into account. The Applicants further submit the claims do not encompass compounds which both inhibit and enhance apoptosis as only compounds which inhibit apoptosis are claimed, and that the claims refer to compound which alter the MMP balance, rather than compounds which both inhibit and enhance MMP balance.

However, the claimed antibody is recited result in "an alteration in the metalloproteinase balance". Accordingly the alteration is for the same function to two different functions as the specification on page 11-12 discloses. It is understood form the specification on page 11-12 that the JB1a results in an inhibition of the apoptotic pathway and an increase in the anabolism of the extracellular matrix. With respect to Dr. Al-Jamal's Declaration, the Examiner enable the specification for the clone JB1a, however, the declaration is not commensurate with the claimed compounds that bind to the beta integrin molecule in a region of amino acid residues 82-87

comprising TAEKLK of the sequence of the mature beta 1 integrin molecule. The Declaration only provided a single example, JB1a antibody, however, the claims are drawn to any compound.

The claimed compounds which cause "alteration in the metalloproteinase balance" are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct agonists or antagonists to accomplish these mutually exclusive endpoints. The term "alteration" indicates a positive or negative change in the balance of the metalloproteinase. The skilled artisan would not have a reasonable expectation that the same compounds that would positively influence the metalloproteinase balance would also serve to negatively influence the metalloproteinase balance as applicant argues.

Applicant submits that Grose appears to teach keratinocytes are not totally dependent on beta 1 integrin to heal wounds, that other integrins appear to compensate at least partially for the lack of beta 1 integrin, that the keratinocytes proliferation rate in beta 1 null keratinocytes is not reduced in early wounds and that the keratinocyte proliferation rate in beat 1 null keratinocytes is increased in late wounds, However, Grose also state that:

> Ultimately, beta1-deficient epidermis did cover the wound bed, but the epithelial architecture was abnormal. These findings demonstrate a crucial role of beta 1 integrins in keratinocyte migration and would re-epithelization.

See Grose at 2303 (emphasis added by Applicant). Grose, therefore, clearly teaches that beta 1 integrin has an important ('crucial") role in repair although this role may be partially compensated for in the absence of beta 1 integrin.

The Examiner agrees with applicant conclusion with respect to Grose findings that beta 1 integrin has an important role in repair although this role is partially compensated (able to be done without β1) for the absence of beta 1 integrin. That means that β1 integrin is dispensable for re-epthelization.

Applicant admits that Zweers teach that alpha 2 beta 1 is dispensable for reepithelization. However, Applicant argues that Zweers also teaches that wound tensile strength was reduced in alpha2 beta 1 null mice which indicates the tissue was less deformable and suggests subtle changes in the organization of the extracellular matrix (see page 474). Applicant concluded that Zweers supports a role for beta 1 integrin in tissue repair. Zweers also states that "in this study, we demonstrate that alpha 2 beta 1 integrin has important, but unexpected, roles I murine cutaneous tissue" (see page 473). It is also noted that Zweers teaches that alpha 2 beta 1 is dispensable for reepithelization, but does not teach that all beta 1 integrin receptor types are dispensable for reepithelization.

However, the scope of the claims is not limited to a particular integrin receptor such as α2β1 for reepithelization, but rather generic to any integrin molecule including α2β1 integrin molecule taught by Zweers. Further, the Examiner points to Clark's (of record) finding that fibronectin and fibronectin receptors (e.g., α5β1) are observed to occur in concert during epidermal

migration over a wounded surface and may perhaps facilitate migration (see page 133S, 1st col., top ¶). Intervention with this process would inhibit such migration and impair tissue repair.

Applicant points to the in vivo treatment regiment with anti-beta 1 antibodies in Dr. Al-Jamal's declaration to promote tissue repair.

The Declaration by Dr. Al-Jamal, filed under 37 CFR 1.132 on 12/28/2009 is insufficient to overcome the rejection under 112(1) enablement because the in vivo data do not commensurate with the scope of the claimed invention. The declaration provides data demonstrating that clone JB1a, is effective in the treatment of Parkinson's disease (in vivo data), arthritis (in vivo data), and alzheimer's (in vitro data), in art accepted models. However, the declaration is limited to JB1a antibody, while the claims claiming any compound that binds to TAEKLK. Further, the Declaration is limited to Parkinson's disease, arthritis and alzheimer's, however, the claims are directed to any and every tissue repair and tissue injury.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 4, 15-16, 20-25 and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US20030109435, as is evidenced by Al-Jamal's declaration, filed 12/28/2009 and Chemicon International catalog no. MAB1965, 9/23/09 (submitted by Applicant on 06/03/2009).

The `435 publication claims a method of inhibiting formation of an amyloid deposit comprising administering an effective dosage of one or more agents that bind to β1under conditions such that the one or more agents inhibit the formation of an amyloid deposit (see published claims 1 4, 14, 21, 50, 53, 70), wherein the agent is an antibody that recognizes the same epitope as an antibody MAV 1965 (claimed clone JB1a) (see published claims 22-39, 71-88), wherein the disease is Alzheimer's disease (see published claims 41, 90) or Parkinson's disease (see published claims 43, 92). The `435 publication teaches that because the meshwork resembled an extracellular matrix, like those formed by integrin, it was investigated whether integrin was present in the HCC; and if so, if integrin facilitated the Aβ meshwork formation on HCC. Gel electrophoresis showed that β1 integrin is expressed in HCC. It was also found that β1 integrin blocking antibodies, including MAB1965 (claimed commercial clone JB1a), could block the Aβ meshwork pattern from forming on HCC (compare FIG. 2A (without antibody) to FIG. 2B (with antibody)). Whether the meshwork pattern was necessary for the toxicity generated by Aβ in these cultures was also investigated. To test this, HCC were incubated with β1 integrin blocking antibodies (AIIB2 (epitope 207-218) and MAB 1965 (epitope 82-87) that had been shown to block the Aβ meshwork. These antibodies also blocked Aβ induced toxicity in a dose dependent manner (FIG. 2C). The antibody AIIB2 is a very potent blocker of Aβ toxicity, exhibiting an IC50 of 170 ng/ml or 1 nM. In contrast, a control antibody had no effect on toxicity (see page 18, example 2).

As is evidenced by Al-Jamal's declaration under ¶5, that administration of JB1a promoted tissue repair in a mouse model of Parkinson's disease.

Catalog No. MAB1965 is the claimed clone JB1a as is evidenced by Chemicon International catalog no. MAB1965.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the clone JB1a.

The reference anticipates the claimed invention.

9. Claims 1, 4, 15-16, 19, 21-25 and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US. Pat. 6,123,941.

The `941 patent teaches and claims methods for reversing malignant phenotype in tissue by administering an effective amount of an β1 integrin function-blocking antibody or a peptide inhibitor of integrin function to the β1 integrin receptors of tissue in need of such treatment (see patented claim 1), wherein the tissue is a tissue expressing β1 integrin receptors (see patented claim 7), wherein the tissue is selected from the group consisting of breast carcinoma tissue, prostate carcinoma tissue, intestinal tissue, or epithelial tissue (see patented claim 8 wherein the .beta..sub.1 integrin function-blocking antibody is a mouse monoclonal JB1a (also referred to as J10: CHIEMICON catalogue #1965) and an antigen binding fragment of monoclonal JB1a (see patented claim 9).

FIG. 9 shows the TUNEL labeling index of day 10-12, bar C shows T-4 tumor cells treated with β1 integrin function-blocking antibody. Non-malignant MEC cells (bar A) respond to an exogenous basement membrane by inhibiting basal apoptosis as evidenced by an apoptotic index of less than 2%. In contrast tumor cells treated with nonspecific Ab (bar B) do not respond appropriately to cues from the ECM and exhibit elevated basal apoptosis rates of greater than 20-30%. Treatment of tumor cells with β1 integrin function-blocking antibody resulted in a significant reduction in basal apoptosis rates of less than 15% suggesting the treatment permitted the tumor cells to respond appropriately to the exogenous basement membrane microenvironment (see col., 13, lines 28-45).

When claim 1 is given its broadest reasonable interpretation: promoting tissue repair can include reversing malignant phenotype in tissue as a result of an inhibition of the apoptotic pathway. The Examiner direct Applicant's attention to the instant specification on page 15, lines 2-21.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the clone JB1a. The reference anticipates the claimed invention.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 15 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over US. Pat. 6,123,941 as in view of Owens *et al* (1994).

The teachings of US. Pat. 6,123,941 have been discussed, supra.

The claimed invention differs from the reference teaching only by the recitation of a chimeric antibody, or a humanized antibody in claim 23.

Owens *et al* teach the modification of murine antibodies such as a chimeric antibody, a single chain antibody, a Fab fragment, a $F(ab')_2$ fragment or a humanized antibody antibodies monoclonal antibody technology, chimeric, single chain, Fab fragments, and $F(ab')_2$. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications, and the chimeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement – dependent cytotoxcity (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by US. Pat. 6,123,941 as chimeric, humanized antibody taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response and the chimaeric antibodies offers the ability to mediate antigen-dependent cytotoxicity and complement-dependent cytotoxcity as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. Claims 1, 4, 15-16 and 19-30 are directed to an invention not patentably distinct from claims 1, 2, 5, 11, 16, 19, 24, 25, 32, 35, 57 and 59-63 of commonly assigned 12528749. Specifically, both applications are using the same antibody clone JB1a that binds amino acid residues 82-84

and possible 179-184 (as is evidenced by Al-Jamal and Harrison, Pharmacology & Therapeutics 120 (2008) 81-101, see Table 1) to teat tissue damage.

13. The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned 12528749, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1, 4, 15-16 and 19-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 11, 16, 19, 24, 25, 32, 35, 57 and 59-63 of copending Application No. 12528749. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are using the same antibody clone JB1a that binds amino acid residues 82-84 and possible 179-184 (as is evidenced by Al-Jamal and Harrison, Pharmacology & Therapeutics 120 (2008) 81-101, see Table 1) to teat tissue damage.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 19, 2010

/Maher M. Haddad/
Primary Examiner
Technology Center 1600